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| 09/095,639 | 06/11/98 | POZZILLI | P 515-4111 |

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DATE MAILED: 09/28/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/095,639 | POZZILLI, PAOLO | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants' Amendment, filed 3/29/00, Paper No. 8, has been entered.

Note that the Examiner of record has changed. The Examiner of record is now Thaian N. Ton of Art Unit 1632.

Claims 1-20 have been canceled. Remarks that are pertinent to the newly added claims that were filed in response to the Office Action mailed on November 22, 1999 (Paper No. 7) will be addressed in present Office Action.

Claims 21-27 are pending and under current examination.

### *Claim Objections*

Claim 23 is objected to because of the following informalities: The claim is not written in proper Markush form. The claims should have an 'and' at the end of part c) and the final line should read: d) mixtures of any combination of a) b) or c). Appropriate correction is required.

Claims 22-25 are objected to because the claims depend on a canceled claim (claim 1). It appears that the claims should depend upon claim 21 and have been examined as such. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-27 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to non-statutory subject matter because they encompass naturally occurring milk. The claims further encompass all non-human milk, such as pig, sheep or goat milk.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to dietary or pharmaceutical products for the prevention of insulin-dependent diabetes, where the product is milk or a product derived from milk which contains non-human β-casein, said β-casein being characterized in that it does not contain SEQ ID NOs: 1 and 2, and methods for the prevention of insulin-dependent diabetes.

The specification teaches that in genetic variants of bovine β-casein, it has been found that a particular hexapeptide sequence elicits an immune response by the production of anti-β-casein antibodies and lymphocytes which recognize such sequences (see p. 2, lines 9-13). The specification further teaches that the presence of

these this hexapeptide sequence which is common to both bovine β-casein and human GLUT 2 in infant formula may cause an immune response where anti-bovine β-casein antibodies recognize GLUT 2 on insulin producing cells. This immune response is thought to lead to onset of insulin-dependent diabetes (see p. 2, lines 13-23). The specification teaches a product derived from milk which is free of non-human β-casein, a product derived from milk comprising at least one β-casein modified from non-human mammals without the hexapeptide sequence, as well as methods, such as the administration through infant formula, of using the product for the prevention of insulin-dependent diabetes (see pp. 5-6 of the instant specification). The specification specifically teaches that the separation of β-casein from acid casein by ion-exchange chromatography (see Example 1), and that the product is then analyzed by chromatography to evaluate the absence of β-casein (see Example 2). The specification further teaches that the product can be purified by diafiltration and lyophilization (see Example 3).

However, the specification fails to teach that administration of the product would provide prevention of insulin-dependent individual in any individual. Cavallo *et al.* (**Lancet**, Vol. 348, Oct. 1996) teach that 51.1% of insulin-dependent (DDM) patients exposed to bovine β-casein responded with a proliferation of T-lymphocytes, whereas only 2.7% of healthy controls showed the same response (see p. 926, col. 1, 3rd paragraph). Cavallo *et al.* teach that sequence homology exists between bovine β-casein and several molecules expressed by insulin-producing β-islet cells, including p69, carboxypeptidase and GLUT 2. In further support of the autoimmune hypothesis of

IDDM, immunological cross-reactivity exists between bovine serum albumin and p69 in IDDM patients, and GLUT 2 autoantibodies have been described in patients with recent onset of IDDM (see p. 927, last paragraph).

Although Cavallo *et al.* teach that T-cell proliferation in human subjects in response to bovine β-casein, there is no evidence that milk without non-human β-casein would prevent diabetes. Furthermore, the cause of diabetes is yet undetermined. Atkinson *et al.* (**Lancet**, Vol. 358, July 21, 2001 pp. 221-229) state that, "The role of genetics versus environment in disease formation has been questioned, and the basis on which type 1 diabetes is characterized and diagnosed in the subject of much debate." (See *Abstract*). In this article, Atkinson *et al.* review the state of the art of the pathogenesis of IDDM. Specifically, with regard to the hypothesis that β-casein is a potential cause of IDDM, Atkinson *et al.* state, "Despite much research, no environmental agent or agents responsible for triggering type 1 diabetes have been uncovered. To date, environmental risk determinants subject to the most widespread investigations can be classified into three groups: viral infections (e.g., coxsackievirus and cytomegalovirus), early infant diet (e.g., breast feeding versus early introduction of cow's milk components) and toxins (e.g., N-nitroso derivatives)." (See p. 222, 2nd column). Atkinson *et al.* further report that there have not been any documented effects on disease of early cow's milk exposure, breast feeding, enteroviral infection and timing of vaccinations. Atkinson *et al.* conclude that,

> Environmental agents may serve as modifiers of disease pathogenesis rather than as triggers. The traditional view of type 1 diabetes postulates that an environmental agent triggers the onset of disease in genetically susceptible individuals. More recent observations support an alternative

> and more complex model (figure 1) wherein the penetrance and expression of heritable immune aberrations (i.e., immune dysregulation), in combination with inherent target organ defects, are part of the life-long influence of multiple environmental factors such as infectious agents, dietary factors and environmental toxins as well as a new class of influencing variables (e.g., sanitation, health-care access and vaccinations). See p. 222-223 bridging paragraph.

In light of many different factors that could potentially be involved in the pathogenesis of IDDM, it could not be predictably concluded that β-casein causes the observed immune response in humans. Furthermore, as stated by Atkinson *et al.* above, it is not clear if β-casein is a modifier of the disease pathogenesis or a trigger of the onset of IDDM. Moreover, the claims are drawn to milk that does not have human β-casein, however, bovine β-casein, which contains the hexapeptide sequence which Applicants argue would elicit the immune response, would still remain in the milk. Additionally, Claim 23 part (c) claims substitution with homologous sequence of human β-casein. It would be expected that a sequence homologous to the hexapeptide sequence would also elicit an immune response.

Applicants argue (on p. 4 of the Amendment filed 3/29/00) that, "It is an established fact that non-human β-casein causes an immune response in humans." Note that the cited post-filing art of Cavallo *et al.* clearly indicates the unpredictability of the state of the art, as Cavallo *et al.* only speculate a role for β-casein in the pathogenesis of IDDM (see p. 927, last sentence); however, the hypothesis is yet unproven and not an established fact. Although Cavallo *et al.* teach that approximately half of patients with IDDM have no apparent immune response to bovine β-casein and

these patients are unlikely to suffer from an autoimmune problem where anti-β-casein antibodies recognize GLUT 2 or any other β-cell antigen, Cavallo *et al.* specifically state that, "β-casein is a good candidate milk protein related to IDDM." This statement is not a statement of fact, but a statement of conjecture.

Applicants further present evidence that there is a strong association between cow's milk consumption and the incidence of IDDM in children (see p. 5, 1st paragraph of response). However, as no such references of record have been provided, the Examiner cannot answer to these arguments. Applicants argue that a number of publications have confirmed the findings that T-cell lymphocyte proliferation response to bovine β-casein and antibodies to bovine β-casein occur in patients with IDDM (see p. 7, 1st paragraph). However, as no such publications of record have been provided, the Examiner cannot answer to these arguments.

Applicants argue that the claims are directed to the prevention of IDDM in all patients, since all individuals at birth can be potentially at risk (see p. 5, 4th paragraph). However, the specification does not provide any teachings which show that administration of the product as claimed would prevent or inhibit the onset of IDDM.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving prevention of IDDM, the lack of direction or guidance provided by the specification to carry out prevention of IDDM in any individual, the lack of working examples, as well as the unpredictable state of the art with regard to the hypothesis of an autoimmune mechanism for IDDM, it would have required undue

experimentation for one skilled in the art to make and/or use the claimed invention and methods of using the same.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21, as written, is confusing. It is not clear which product contains non-human beta casein (milk, or a product derived from milk). Furthermore, it is not clear if the product which contains the non-human beta casein additionally contains human beta casein. Additionally, it is not clear what sequence the product does not contain, as the claim recites the term, "the sequence" in line 5 of the claim, yet two sequences follow. Appropriate correction is requested.

Claim 22, as written, does not further limit the claim. Furthermore, it is not clear if the sequences in the claim are to be contained or not in the product.

Claim 22 recites the limitation "the sequences" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 23, as written is confusing. The claim recites the term, "some of all" in part (a) of the claim. Clarification and/or amendment is requested.

Claim 23 recites the limitation "said sequences" in parts (b) and (c). There is insufficient antecedent basis for this limitation in the claim.

Claim 23 is confusing, as it recites the term, "said sequences" in parts (b) and (c), but it is not clear which sequences these are referring to.

Claim 24, as written, is confusing, because it recites the phrase, "synthetic proteins lacking the sequence" in line 5 of the claim. It is not clear which of the two provided sequences, or both, the synthetic proteins are lacking. Appropriate correction is requested.

Claim 26 recites the limitation "the new born and infants" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claims 25-27 are drawn to methods for preventing insulin-dependent diabetes, but the claims fail to recite appropriate process steps detailing how to prevent insulin-dependent diabetes. For example, in claims 25-26, it is not clear how the administration of a product relates to the preamble, "A method for preventing insulin-dependent diabetes." Furthermore, claim 27 recites a method by obtaining the recombinant human beta casein by cloning methods (see lines 2-3 of the claim); however, the claim recites no steps involving gene expression or protein isolation. Cloning methods can only result in the isolation of clones or the production of organisms.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 21, 22, 23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Friedman (US Pat No. 4,501,585, published 2/26/1985).

The claims are directed to a dietary or pharmaceutical product for the prevention of insulin-dependent diabetes, said product comprising milk, or a product derived from milk which contains non-human β-casein, said casein does not contain SEQ ID NO: 1 and SEQ ID NO. 2. The claims are further directed to a method for preventing insulin-dependent diabetes comprising the administration of the product to infants and newborns.

Friedman teaches a harvesting device to collect mother's milk and can be used to nurse infants. (See *Abstract* and col. 4, lines 55-60).

Accordingly, Friedman anticipates claims 21, 22, 23 and 25.

Note that in analyzing these claims, the intended use, a method for preventing insulin-dependent diabetes, does not provide patentable weight in a 102 rejection.

Claims 21 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimatani *et al.* (US Pat No. 5,084,285, published 1/28/1992).

Claim 21 is directed a dietary or pharmaceutical product for the prevention of insulin-dependent diabetes, said product comprising milk, or a product derived from milk which contains non-human β-casein, said casein does not contain SEQ ID NO: 1 and SEQ ID NO. 2. Claim 23 is directed to a dietary or pharmaceutical product wherein the casein sequence has modified amino acids, removed amino acids, substituted amino acids, or a combination of any of the above.

Shimatani *et al.* teach a process of desalting raw milk, such as goat's milk or sheep's milk (see col. 2, line 43).

Accordingly, Shimatani *et al.* anticipate claims 21 and 23.

Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Rosen (US Pat No. 5,304,489, published 4/19/1994).

Claim 24 is directed to a dietary or pharmaceutical product according to claim 1, further comprising vegetable and/or animal and/or synthetic β-caseins with peptides derived from the hydrolysis from the hydrolysis of an animal, vegetable and/or synthetic proteins lacking the sequence SEQ ID NO. 1 and SEQ ID NO. 2, and mixtures thereof.

Rosen teaches the production of transgenic mice expressing rat β-casein in its milk (see col. 9, lines 59-64 and col. 12, #3).

Accordingly, Rosen anticipates claim 24.

Claims 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergstrom *et al.* (WO 93/04171, published 3/4/1993), cited in this application.

Claims 26-27 are directed to a method for preventing insulin-dependent diabetes comprising the administration of a milk containing recombinant human β-casein to the newborn and infants, wherein the recombinant human β-casein is obtained by cloning methods, using yeast, bacteria, fungi, or from transgenic animals.

Bergstrom *et al.* teach a DNA sequence encoding human β-casein and analogues of the DNA sequence (see *Abstract*). Bergstrom *et al.* teach milk from a non-human transgenic mammal comprising recombinant human β-casein. The transgenic mammal's natural β-casein gene has been replaced by an expression construct that encodes the human β-casein gene (or an analogue). Bergstrom *et al.* teach that it the recombinant human β-casein of the invention can be used for feeding infants (see *Abstract*).

Accordingly, Bergstrom *et al.* anticipate claims 26-27.

Note that in analyzing these claims, the intended use, a method for preventing insulin-dependent diabetes, does not provide patentable weight in a 102 rejection.

Claims 26-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Slattery (US Pat No. 5,795,611, filed 12/20/1989).

Slattery teaches a method of producing recombinant human β-casein from *E. coli* (see col. 2, lines 38-47), as well as animals. Slattery further teaches the feeding of milk comprising recombinant human β-casein to infants and newborns.

Accordingly, Slattery anticipates claims 26-27.

Note that in analyzing these claims, the intended use, a method for preventing insulin-dependent diabetes, does not provide patentable weight in a 102 rejection.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

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